GENE THERAPY ADVISORY COMMITTEE

SIXTH ANNUAL REPORT

January 1999 – December 1999

Health Departments of the United Kingdom
2000

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2000

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FOREWORD

The first gene therapy clinical trial to be approved started in September 1990. Since then, more than 400 clinical protocols have been approved worldwide. More than 10% of these have taken place in the UK, accounting for around 50% of all European studies. Applications to GTAC this year have focussed on gene therapy approaches to develop potential treatments for cancer.

As we reach the end of this first decade of gene therapy research, I am pleased to note encouraging evidence of positive clinical results has emerged from trials for severe combined immune deficiency (SCID-IX) and for haemophilia. As well as for its successes, the past year will also be remembered as that in which the first gene therapy treatment-related death occurred in the USA. In September 1999 an 18-year-old man died as a consequence of participating in a phase I gene therapy trial using an adenovirus vector to correct an ornithine transcarbamylase deficiency (OTC), serving to highlight the importance of effective and efficient monitoring of patients involved in gene therapy trials.

In the spring of 1999 GTAC had already commenced a review of serious adverse events and issues related to the monitoring of patients involved in gene therapy research. As a consequence of information received in relation to the USA OTC study, the GTAC review focussed on the adenoviral gene therapy trials. Although no major life-threatening toxicity had occurred with the use of adenoviral vectors, it was decided to convene a working group to develop recommendations for patient monitoring in adenoviral gene therapy studies.

GTAC has been concerned about the lack of provision for long-term follow-up of patients who have received gene therapy. This year, with the co-operation of clinical investigators, GTAC have established a confidential mechanism which will operate via the National Health Service Central Register and provide for the long-term follow-up of UK participants in gene therapy research.

Gene therapy clinical trials must continue to be conducted to the highest scientific and ethical standards with patient welfare and safety being paramount. GTAC's first guidance notes were published in 1994 and I welcome the publication of GTAC's updated guidance to proposers. I wish to take this opportunity to thank the NETS subgroup of GTAC for their input into updating the guidance notes for investigators and reviewing the new developments.

GTAC also owes enormous gratitude to the external experts who review proposals to conduct gene therapy research and to the expert advisors with whom the Committee consult. I would like to take this opportunity to thank all our external advisors for their efforts over the reporting year.

Finally, it gives me immense pleasure to welcome Dr Sohaila Rastan, Ms Caroline Benjamin and Mr Michael Harrison, who joined GTAC in December 1999.

Professor Norman C Nevin
2000

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GTAC Sixth Annual Report

PART 1

SECTION 1 – PROTOCOLS APPROVED BY GTAC (1999)

1.1 GTAC met 4 times during 1999 and assessed a total of 7 new protocols in committee. The Committee was satisfied for 5 of these research projects to proceed. The two studies for which approval was pending at the end of 1999 are recorded in Section 3.

1.2 In addition, the Committee received a number of requests from investigators to make amendments to existing approved gene therapy protocols. Whenever appropriate these were dealt with either by agreement with the Chairman or by postal circulation to Committee members. These are recorded in Section 2.

MALIGNANT MELANOMA

1.3 Primary cutaneous malignant melanoma (skin cancer) has been increasing in prevalence over the past two decades. As awareness has increased more patients have been diagnosed at an early, surgically curable stage.

1.4 Over 7,000 patients per year in the US and a similar number in Europe eventually die of the disease if it has spread. Chemotherapy can help alleviate symptoms for patients with advanced disease but a significant overall effect on survival has not been demonstrated for patients with metastatic disease.

Phase I trial of immunotherapy with adenovirus-interferon-γ (TG1041) in malignant melanoma. St George's Hospital, London. (GTAC 033)

1.5 Adenoviruses cause infections of the respiratory tract. The vector TG1041 is a replication-defective adenovirus (altered so that it cannot cause infections) which contains a gene for human Interferon-γ (IFN-γ).

1.6 IFN-γ belongs to a class of molecules called cytokines whose function is to regulate immune response. IFN-γ is normally produced by white blood cells that fight infection and disease. In addition, IFN-γ is also able to enhance the immune system's ability to recognise and destroy tumour cells but a barrier to its therapeutic use is that it is very toxic when given at levels high enough to provoke a response.

1.7 In this study the investigators seek to overcome this toxicity by introducing the gene for IFN-γ into one of the patient's tumours with the aim of stimulating an anti-tumour immune response to attack the injected tumour and distant metastases.

1.8 This study was initially considered and rejected by GTAC at their meeting on February 10. The concerns of the Committee were subsequently addressed by the proposers and approval was granted following reconsideration of a revised protocol at their meeting on 12 May.

HEAD & NECK CANCER

1.9 Head and neck cancers make up about 4% of all cancers in the UK. Risk factors for head and neck cancer include tobacco smoking or chewing and alcohol consumption. These cancers are more common in men but the incidence has fallen over recent years, perhaps due to better oral hygiene and less tobacco and spirit consumption.

1.10 If detected early, irradiation and surgery can lead to good results. However, at advanced stages radical treatments involving mutilating surgery, irradiation, or chemotherapy produces poor results. Recurrence of these tumours reduces the patient's quality of life as well as reducing their chances of survival.

LIVER CANCER

1.11 Colorectal cancer is the second most common cause of cancer related deaths in the UK. It accounts for 28,000 new cases and 19,000 deaths annually.

1.12 Surgery offers the only form of curative treatment, but has to be performed before there is tumour spread. The most common site for metastases is in the liver. In a small proportion of patients surgical removal of the liver tumour may be successful but the overall prognosis for the majority of patients with colorectal liver metastases remains poor.

Protocol 1: Gene Directed Enzyme Pro-drug Therapy for the Treatment of Head and Neck Cancer. GTAC 031

Protocol 2: Gene Directed Enzyme Pro-drug Therapy for the Treatment of Liver Cancer. Queen Elizabeth Hospital, Birmingham. GTAC 032

1.13 At their meeting on 11 May, GTAC considered two protocols which utilise Gene Directed Enzyme Pro-drug Therapy (GDEPT); for head and neck cancer and for liver metastases from colorectal cancer.

1.14 The pro-drug CB1954 can be activated by an enzyme called nitroreductase (NTR) to a potent agent which damages DNA and kills cells regardless of cell type or whether or not they are dividing.

1.15 The principle of GDEPT is to deliver a gene coding for the pro-drug converting enzyme to the tumour cells. The patient is then dosed with the pro-drug and the cells infected with the gene therapy vector should produce the enzyme, convert the pro-drug to its toxic form and die.

1.16 Humans do not make the NTR enzyme. A bacterial NTR gene has been engineered into an adenovirus vector (Ad5) where its expression is under the control of the CMV promoter (in order to direct high levels of enzyme production within infected tumour cells).

1.17 Following submission of revised versions of the protocols addressing issues raised by the Committee, GTAC granted approval for the studies to commence on 14 July.

A Phase II Trial of Preoperative Intratumoural Injection with Onyx-015 in Patients with Resectable Squamous Cell Tumours of the Head and Neck. Western Royal Infirmary, Glasgow. GTAC 035

1.18 Loss of the function of a tumour suppressor gene called p53 is the most common type of genetic abnormality found in human cancer cells. Onyx-015 is an adenovirus that has been modified (attenuated) so that it cannot replicate in normal cells but efficiently reproduces in and kills p53 deficient tumour cells. This selectivity has been achieved by removing a part of the viral genome which encodes a protein whose normal function is to bind and inactivate the p53 gene product in the infected cell. Onyx is therefore unable to efficiently replicate in normal cells but there is no barrier to its replication in p53 deficient tumour cells.

1.19 In this study, patients' tumours will be injected with Onyx-015 prior to surgery. The surgically removed tumour will then be studied to see whether the virus has spread within the tumour causing tumour cell death.

1.20 The proposal was considered by GTAC at their meeting on 14 July and granted conditional approval subject to minor amendment of the protocol. Full approval was subsequently granted on 27 July 1999.

GLIOBLASTOMA

1.21 Gliomas account for half of all brain tumours and the most common of these is glioblastoma (GB). Malignant gliomas occur in around 3-5 per 100,000 of the population per year. Despite aggressive therapy, including surgery, the median survival for patients is less than one year.

A study of the potential for efficacy of the modified *Herpes simplex* virus 1716 following intratumoural injection into primary malignant glioma. Beatson Oncology Centre, Glasgow. GTAC 018A

1.22 The *Herpes simplex* virus causes infections such as cold-sores, genital infections and a rare brain infection (encephalitis). *Herpes simplex* 1716 has been modified so that it is incapable of infecting or multiplying in cells that are not themselves rapidly dividing. Most of the cells in the normal brain do not divide at all but the rapidly dividing tumour cells will be susceptible to infection by HSV 1716 and therefore should be selectively killed by the virus.

1.23 In December of 1996 the proposers were granted approval for a Phase I dose escalation study of intratumoural injection of HSV 1716 into malignant glioma in patients whose disease had relapsed. This study showed HSV 1716 to be safe when injected into patients' tumours at doses up to 10^5pfu.

1.24 Approval for the second part of this study, to recruit a maximum of 12 patients with newly diagnosed glioma prior to surgery, was approved on 16 July 1999.

OVARIAN CANCER

1.25 Ovarian cancer is considered the most difficult gynaecological cancer to prevent or cure because it is notoriously silent at onset and is usually diagnosed in an advanced stage.

1.26 World-wide there are over 50,000 cases of ovarian cancer per year. Current standard treatment includes surgery to remove all or most of the tumour followed by chemotherapy but this approach cures less than half of the patients. Ovarian cancer is the leading cause of cancer related deaths in women.

A Phase II/III trial of chemotherapy alone versus chemotherapy plus SCH58500 in newly diagnosed stage III ovarian cancer patients with less than 2cm residual disease following surgery. The Royal Marsden, Sutton, Surrey. GTAC 034

1.27 Up to 80% of ovarian tumours have an abnormal gene called "mutant p53" which is believed to play a part in tumour growth. In this study, an adenoviral vector will be used to introduce a "wild-type" or normal copy of p53 into the cancerous cells, therefore suppressing tumour growth.

1.28 SCH58500 is a disabled adenovirus (adenoviruses normally cause infections of the respiratory tract but this virus has been altered so that it is incapable of setting up an active infection) carrying wild-type p53. The virus has been engineered to produce high levels of the p53 protein within cells (expression is under the control of the CMV promoter).

1.29 Patients will be randomised to either chemotherapy alone (taxol/carboplatin) or in combination with SCH58500. Five cycles of treatment will be administered to allow sequential layers of tumour cells to be targeted if each treatment successfully removes an outer layer of tumour.

1.30 This proposal was considered by GTAC at their meeting on 12 May and Conditional Approval was granted for the proposed work, subject to receipt of satisfactory responses to a number of points. Approval for the study was subsequently granted on 19 July 1999.

SECTION 2 – PROTOCOLS STILL UNDER CONSIDERATION AT THE END OF 1999

Gene therapy protocol for the use of MetXia-P450 for the treatment of ovarian cancer. Northern General Hospital, Sheffield. GTAC 030

2.1 MetXia-P450 is a retroviral vector carrying the human gene for cytochrome P450 which is an enzyme that converts the pro-drug cyclophosphamide to an agent which is highly toxic for cells that are undergoing DNA replication, such as tumour cells. Cyclophosphamide has been used extensively for the treatment of a number of cancers, including ovarian cancer. Under these circumstances the liver activates the drug which is then dispersed to tumours via the blood stream. A major limitation of the conventional approach is that low doses do not kill all the tumour cells and high doses are toxic to the bone marrow of the patient.

2.2 The investigators proposed to administer MetXia-P450 by a single intraperitoneal injection prior to chemotherapy (cisplatin and cyclophosphamide). In this way, the investigators hope to increase the level of the active drug locally and therefore enhance the tumour killing capacity of relatively low doses of cyclophosphamide.

2.3 Patients were to be divided into four groups, the first two receiving MetXia P450 and a therapeutic dose of carboplatin. Following surgery samples of their tumour would be assessed to see which dose had resulted in the greatest uptake of virus by the tumour cells. Groups 3 and 4 would then receive the dose which resulted in maximum gene transfer together with cyclophosphamide and carboplatin.

2.4 GTAC considered this proposal at their meeting on 12 May 1999. Conditional Approval was granted subject to receipt of a satisfactory response to a number of points and amendments to the protocol. At the end of 1999 these issues remained to be resolved.

Clinical Proposal for an Angiogenic Gene Therapy Product For Peripheral Arterial Occlusive Disease (PAOD). St George's Hospital, London. GTAC 036

2.5 Peripheral arterial occlusive disease (PAOD) causes a narrowing of the blood vessels in the leg, due to deposits on the blood vessel walls (atherosclerosis). Because the blood flow to the patient's limb is reduced they experience pain in the leg and foot. As the disease worsens other symptoms can develop, including difficulty in walking, permanent pain, and ulceration and gangrene in the affected leg.

2.6 For some patients it is possible to reduce or by-pass the blockage surgically but PAOD can result in amputation of the affected limb and may also be life-threatening. Patients may also be given drugs which dilate the blood vessels or prevent clot formation but these don't tend to improve the ultimate outcome (amputation or death) for many of the very ill patients.

2.7 A number of investigators have previously shown that the fibroblast growth factor 4 (FGF-4) protein is able to promote the growth of new blood vessels. The investigators plan to use an adenoviral vector (similar to viruses which cause colds but disabled so that they cannot replicate) to deliver the gene for FGF-4 into the muscles of the patients affected leg (this is called Ad5.FGF-4).

2.8 It is hoped that the cells of the patient's muscles will make the FGF-4 protein thereby promoting the blood flow and formation of blood vessels. It is hoped that if this happens, the progression of the disease may be slowed or halted and also that the patient's symptoms might improve (healing of leg ulcers, reduction in pain etc).

2.9 This is a set of "double-blind, randomised, placebo-controlled study" which means that some of the patients would be injected with Ad5.FGF-4 and some with a placebo (consisting only of the liquid used to suspend the vector). Neither the patient, nor the person injecting the liquid will know whether the vial used contains vector or not.

2.10 GTAC considered this proposal at their meeting on 15 December 1999. The Committee deferred their decision subject to the receipt of further pre-clinical data from studies already underway.

SECTION 3 – AMENDMENTS TO PREVIOUSLY APPROVED PROTOCOLS

3.1 **Intratumoural injection of Herpes simplex virus HSV ICP 34.5 into accessible soft tissue nodules of secondary malignant melanoma. Glasgow Western Infirmary. GTAC 026.** The protocol was extended for registration of patients from those aged 18-70 to those aged 18-80 years (4th January 1999). The protocol was amended to allow patients to enter this trial who have subcutaneous nodules but no evidence of lesions elsewhere. In addition approval for re-entry into the trial of a single patient following evidence of dramatic effect of his injected nodule (10 February 1999).

3.2 **Study evaluating the safety and the gene transduction into malignant cells after the administration of E1A-lipid complex by intra-peritoneal administration in patients with epithelial ovarian cancer who overexpress HER-2/neu. John Radcliffe Hospital. GTAC 022.** Approval was granted to extend the study to the Royal Surrey County Hospital on 12 February 1999.

3.3 **A multiple ascending dose study evaluating the safety and gene transduction into malignant cells after the administration of E1a lipid complex by intra-tumoral injection in patients with unresectable or metastatic head and neck tumours. Royal London Hospital. GTAC 025.** The study submission was withdrawn by the proposers with effect from 14 January 1999.

3.4 **Study of hepatic artery infusion with wild-type p53-CMV-AD in liver tumours. Hammersmith Hospital. GTAC 028.** The study was considered by GTAC at their meeting in October 1998 and was granted conditional approval, subject to receipt of satisfactory responses on a number of points, on 9 November 1998. A suitably amended protocol was submitted (dated 9 February 1999) and approval for the proposed work to commence was granted by Chairman's action on 24 February 1999.

3.5 **A Pilot Study of Idiotypic Vaccination for Follicular B-Cell Lymphoma. Royal Bournemouth Hospital. GTAC 029.** A set of 15 minor amendments to the protocol and the patient information leaflet were approved on 11 October.

3.6 **A Phase II Trial of Preoperative Intratumoural Injection with Onyx-015 in Patients with Resectable Squamous Cell Tumours of the Head & Neck. Beatson Oncology Centre, Glasgow. GTAC 035.** Approval was granted on 30 September for an amendment permitting additional pre-screening and pre-surgery blood tests.

SECTION 4 – REGULATORY ISSUES

Long-Term Monitoring of Patients Participating in Gene Therapy

4.1 Gene therapy is a very new approach which it is hoped will lead to new treatments for disease. Gene therapy has been given to in excess of 3000 patients world-wide and every effort is made to be sure it is safe. However most of these patients will have been lost to long-term follow-up as there is (to our knowledge) no established mechanism to allow their health to be monitored in the longer term. It will not be until more patients have received gene therapy and over a longer period of time that we can be totally confident that the approach is safe.

4.2 For these reasons, the GTAC would like to monitor patients' health in the long-term, especially after they have completed the gene therapy study (when many patients may loose contact with the study doctor). In theory, gene therapy could affect the next generation. Because of this small possibility, GTAC would also like to monitor the health of any child born to a person who has participated in a gene therapy trial until they are 16 years old.

4.3 The doctors conducting gene therapy studies will be asked to provide to the Office of National Statistics (who keep a record of NHS numbers) a code number for their gene therapy study together with a separate number specific to each patient. These two code numbers will be entered into the patient's NHS record. This process is called "flagging". Flagging is not unusual. Currently, NHS records may be flagged to indicate patients' participation in a number of studies and may also occur when a person is diagnosed with certain diseases.

4.4 All information supplied to the Department of Health will be linked only to the patient's NHS number. Personal details (such as names or addresses) will not be supplied and the patient's identity will not be disclosed. Because the NHS record is flagged it will be possible for the Department of Health to indirectly make inquiries about the patients' health by writing to their GPs. It is intended that a pilot scheme be launched so that it will also be possible to find out whether any of these patients had had children since receiving gene therapy.

4.5 Patients will be asked for their consent to long-term follow up. Whilst GTAC will not seek direct contact, any patient who would like further details of the study or clarification on any point is welcome to contact the GTAC Secretariat.

4.6 The monitoring study has been considered and approved by the relevant ethics committee (South Thames Multi-Centre Ethics Committee) and it is expected that the programme will be rolled out over summer 2000.

GENE THERAPY DEATH IN USA

4.7 In September 1999 the death of a study volunteer, Jesse Gelsinger, in a gene therapy research study at the University of Pennsylvania's Institute for Gene Therapy, raised concerns about the safety of adenoviral vectors in gene therapy, especially when administered to blood supply of the liver. Mr Gelsinger had an inherited disorder called Ornithine Transcarbamylase Deficiency (OTC), that meant his liver was unable to break down ammonia.

4.8 The study involved delivering an adenoviral vector carrying the OTC gene into the patient's liver by way of direct injection via the hepatic artery. The purpose of the study was to determine the maximum safe dose and Mr Gelsinger received the highest scheduled dose. The procedure went uneventfully but over the following 4 days his condition deteriorated rapidly and the patient died.

4.9 US researchers submitted all relevant data for consideration by the Recombinant DNA Advisory Committee (RAC) at their meeting on 8-10 December. The meeting revealed that the team at the Pennsylvania Institute may have seriously breached regulatory protocol. Mr Gelsinger's death further raised concerns about potential under-reporting of adverse events to the regulatory authorities and the oversight of gene therapy clinical trials in the USA.

4.10 The RAC three-day meeting took place just weeks after President Clinton requested that the RAC and the FDA (Food and Drug Administration) determine how patients could be better protected in gene therapy trials and Senator Bill Frist held the first of a series of hearings on gene therapy oversight.

4.11 While there is no conclusive answer as to why Jesse Gelsinger died, University of Pennsylvania researchers and others believe he experienced an extreme immune reaction, mostly likely to the vector, perhaps combined with a parvovirus infection and malfunctioning liver.

4.12 In spring of 1999 GTAC began a review of serious adverse events reporting and issues related to the monitoring of gene therapy patients. As events unfolded in the USA in relation to the death of a patient enrolled for gene therapy in an adenoviral study, the GTAC review was concentrated on UK adenovirus studies. At the time of the survey 69 patients, all with advanced cancer, had been recruited into 11 adenoviral gene therapy studies.

4.13 GTAC subsequently agreed to conduct a more detailed review of UK studies and to convene an ad hoc adenovirus working group whose membership was drawn from GTAC, other regulatory bodies the research community. One study with approval in the U.K. which had yet to recruit patients involved the administration of adenovirus via the hepatic artery. The investigator was therefore asked not to recruit into this study until it could be reconsidered in the light of adenovirus working party recommendations.

4.14 The working party met in Spring 2000 and at the time of publication of this Annual Report their recommendations have been published as supplementary guidance to UK adenoviral gene therapy researchers.

Report of an inquiry into allegations relating to gene therapy for patients with liver cancer chaired by Sir Thomas Boyd-Carpenter

4.15 In June 1999 GTAC were informed of a number of serious allegations concerning the administration of gene therapy to patients with liver cancer. The investigator concerned was asked, in June 1999, to refrain from recruiting patients into their GTAC approved study.

4.16 In July 1999 an NHS Inquiry was set up by the London Regional Office of the NHS Executive, acting on behalf of the Secretary of State to investigate the allegations. Most of the allegations had their provenance in Denmark, where inquiries had also taken place. The Inquiry Panel gathered written and oral evidence from the UK, Denmark and the USA. Several of the allegations were withdrawn as unfounded before the inquiry began, and these are described in the relevant chapters of the report. A number of issues were identified where improvement was recommended. The report (dated January 2000) is available from:

NHS Executive
London Regional Office
40 Eastbourne Terrace
London
W2 3QR

SECTION 5 – THE GTAC NEW & EMERGING TECHNOLOGIES SUBGROUP (NETS)

5.1 The GTAC *Guidance to Proposers* was published in 1994. The intervening years have witnessed the evolution of many new technologies related to gene therapy. NETS were asked to review the current status of gene therapy research and to update the guidance to investigators seeking to carry out gene therapy research in the United Kingdom.

5.2 NETS met on 11 October 1999 to discuss considerations related to new technologies and developments in gene therapy and to consider what amendments to GTAC's guidance notes will be necessary to bring the document up to date. In addition to considering developments of the past 6 years, NETS were asked to consider technologies that may have a significant impact on the nature of gene therapy in coming years. At this initial meeting (planned to be the first of two) the following emerging technologies were discussed:

Gene Therapy of Mitochondrial Disorders

5.3 Mitochondria are small structures within each cell that act as energy generators. When mitochondria are not working correctly a disease may result and the most commonly affected organs are those which require a lot of energy to function such as the brain, heart and skeletal muscle.

5.4 Mitochondria contain their own genome which carries genes containing the genetic message for several critical components of the energy-making pathway. Novel approaches are being developed to allow the introduction of DNA into mitochondria thereby opening up the possibility of developing gene therapies for diseases caused by defects in mtDNA.

The use of antisense and ribozymes in gene therapy

5.5 Certain diseases or disorders could be prevented or treated if it were possible to "switch off" or inactivate the relevant disease-causing gene.

5.6 Antisense and ribozyme technologies both aim to interrupt the normal informational flow by which gene products are made. RNA is the intermediate molecule in the chain between DNA and protein and it carries the "message" or instructions contained within the gene to the cell's protein making machinery.

5.7 Antisense is itself nucleic acid and is able to bind to this message in a specific manner and prevent it being "read". Antisense may be introduced directly into cells in the form of short stretches of nucleic acid or can be produced within the cell from templates carried on gene therapy vectors.

5.8 Ribozymes are molecules of RNA that specifically recognise a defined RNA message and chop it up, thereby destroying the message before the protein has been made.

Genetic Vaccines

5.9 Vaccines made of DNA or RNA are a form of gene therapy that uses the patients' own cells to make proteins that stimulate an immune response. This type of vaccine is being developed against a number of viral, bacterial and parasitic diseases as well as certain types of cancers.

5.10 A number of studies are already underway in the UK in which patients are vaccinated against tumour-specific antigens with the intent of breaking immunological tolerance and leading to the generation of tumour-specific immune responses.

Gene Repair

5.11 Genetic mutations or "spelling errors" in genes can lead to disease. To date, the majority of gene therapy approaches to treat such diseases have focussed on delivering extra normal copies of the affected gene into cells. Cells have a DNA repair system which can detect and correct errors (similar to the spell checker on a computer).

5.12 DNA repair has been dubbed "chimeraplasty", because it relies on hybrid molecules of DNA and RNA called chimeras. In essence, these molecules contain DNA with the correct version of the spelling error which can pair up with the defective gene and trick the cell's DNA repair machinery into correcting the error.

5.13 Chimeraplasty has proven effective in correcting gene defects in mammalian cells in culture as well as in animal models of disease. In principle this technique could be used to develop treatments for a wide range of inherited disorders.

SECTION 6 – REFERENCES

[1] Gene Therapy Advisory Committee: First Annual Report January 1994-December 1994. Health Departments of the United Kingdom. London. Department of Health. 1995.

[2] Gene Therapy Advisory Committee: Second Annual Report January 1995-December 1995. Health Departments of the United Kingdom. London. Department of Health. 1996.

[3] Gene Therapy Advisory Committee: Third Annual Report January 1996-December 1996. Health Departments of the United Kingdom. London. Department of Health. 1997.

[4] Gene Therapy Advisory Committee: Fourth Annual Report January 1997-December 1997. Health Departments of the United Kingdom. London. Department of Health. 1998.

[5] Gene Therapy Advisory Committee: Fifth Annual Report January 1998-December 1998. Health Departments of the United Kingdom. London. Department of Health. 1999.

SECTION 7 – GLOSSARY

Adenovirus / adenoviral

A DNA virus, usually associated with mild upper respiratory tract infections.

DNA (deoxyribonucleic acid)

The chemical (nucleic acid) substance in chromosomes and genes in which genetic information is coded.

Chemotherapy

Treatment with chemicals that destroy cancerous tissue.

Cell

The smallest unit of living organisms. It has been estimated that the body of a human adult comprises 50 million, million cells.

Cytotoxicity

The property of being able to directly kill cells.

Gene

Genes are the biological units of heredity – a sequence of DNA which codes for one *protein*. It has been estimated that the human genome comprises in excess of 40000 genes.

Genetic disease or disorders

Conditions which are due to defects in the genetic constitution of an individual. They may be the direct consequences of defects in single genes; or in whole chromosomes, parts of which may be lost, duplicated or misplaced; or due to the interaction of multiple genes.

Germline cells

Cells in embryonic life that become sperm in males and eggs in females and transmit genetic information to the next generation.

Herpes simplex

The virus responsible for causing cold-sores.

Immune response

A specific white blood cell or antibody response against an antigen (protein).

Immunomodulation

The use of a drug to alter, suppress of strengthen the body's immune system.

Intraperitoneal

Within the cavity that contains the abdominal organs.

In Utero

In the womb (uterus)

Malignant

Cells that have lost their normal control mechanisms and develop into a cancer.

Metastatic, metastases

Cancer which has spread from the site of the original tumour to other tissues/organs in the body.

Placebo

A dummy treatment compared to which an experimental treatment must produce better results in order to be considered effective.

Prodrug

Relatively inert compounds that can be converted to an active or toxic form.

Promoter

A short piece of DNA contiguous with a gene which controls whether or not (and at what rate) the corresponding *protein* is produced.

Protein

Proteins are essential constituents of the body that are coded for by DNA. They form the structural materials of muscles, tissues, organs, and are regulators of function, as enzymes/hormones.

Proto-oncogene

Genes which play a role in cell division. There is evidence to suggest that certain cancers are caused by activation (switching on) of these genes.

Retrovirus / retroviral vector

A type of virus used in gene therapy as a vector. Such viruses are usually animal viruses rather than agents of human disease. They are made inert so that they can enter a human cell carrying a gene for gene therapy without causing disease

Somatic Cell

The cells which make up the body of an individual excluding the egg or sperm cells.

Stem Cells

A cell that can self renew and produce all the types of cells.

Tumour regression

A cancer that has become smaller or has completely disappeared.

Tumour suppressor genes

Such genes produce proteins to regulate the rate at which cells divide. The absence or dysfunction of a tumour suppressor gene is associated with the production of cancer cells.

Unresectable

Unable to be fully removed by surgery.

Vaccinia

A member of the family of DNA-containing viruses which also includes smallpox virus. It was the standard vaccine against small pox.

Vector

A carrier, usually a virus or lipid, to transport foreign DNA across the cell membrane into the cell.

Virus

A protein covered DNA or RNA containing organism which is only capable of reproducing within a host cell. Some viruses cause disease, such as chicken pox or influenza. Viruses suitably modified can be used as means of delivering a gene into cells.

Guidance on making proposals to conduct Gene Therapy Research on human subjects

PART 2

SECTION 1 – GENE THERAPY RESEARCH ON HUMAN SUBJECTS

Introduction

1. This document gives guidance on the procedures that should be followed in the United Kingdom when proposals are made to conduct gene therapy research on human subjects. It details the information that should be submitted in order to enable the Gene Therapy Advisory Committee (GTAC) to assess the acceptability of gene therapy research proposals.

2. Some guidance is also given on the requirements of other regulatory bodies or committees, including Local Research Ethics Committees, the Medicines Control Agency, the Health and Safety Executive and the Department of Environment, Transport and the Regions.

3. The guidance should be read in addition to general guidance on clinical trials and research governance in the NHS (see Further Reading).

4. Supplementary guidance and reports have been issued by GTAC in relation to monitoring of patients enrolled in adenoviral gene therapy studies and *in utero* gene therapy. Both can be obtained as stand-alone documents from the GTAC web-pages. (www.doh.gov.uk/genetics/gtac.htm).

GTAC review process

5. GTAC reviews proposals to conduct gene therapy research and provides advice in related areas. GTAC reviews are in addition to those of local research ethics committees (LREC), whose roles and responsibilities are unchanged.

6. GTAC approval should be obtained before NHS personnel conduct any gene therapy research on human subjects, whether conducted on NHS or other premises, in the UK. GTAC approval should also be sought where any part of gene therapy research on human subjects takes place in the UK. This would include enrolment, monitoring, follow-up and other study related procedures. NHS personnel who conduct gene therapy research overseas are encouraged to submit protocols to GTAC for information (this should include any information that will be given to prospective participants).

7. GTAC expects applicants to provide a full account of what is proposed. This should place particular emphasis on the ethical aspects, including an assessment of the scientific merit and safety of the proposed work.

8. In conducting such reviews, GTAC continues to reflect the principles established by the Clothier committee, namely that:

- gene therapy is research and not innovative treatment;
- only somatic therapy should be considered. Germ line interventions are considered to pose unacceptable safety and ethical concerns;
- patients should take part in gene therapy research trials only after a full explanation of the procedures, risks and benefits and after they have given their informed consent, if they are capable of doing so; and
- therapeutic research involving patients must not put them at disproportionate risk. For this reason gene therapy should be restricted to patients with serious disorders where current alternative treatments are not wholly effective.

Definition of gene therapy

9. GTAC has reviewed and revised the 1994 definition of gene therapy in the light of experience and of definitions established by other countries and international bodies. GTAC wishes to maintain a wide definition of gene therapy in order not to exclude certain novel approaches from GTAC oversight. Within the context of GTAC's terms of reference, gene therapy can be defined as:

> The deliberate introduction of genetic material into human somatic cells for therapeutic, prophylactic or diagnostic purposes.

10. This definition is intended to include studies involving the use of most of the established

techniques for delivering genes into cells. A non-exhaustive list of examples includes genetically modified viral vectors, liposome-encapsulated DNA, anti-sense techniques, naked DNA injection, DNA-mismatch repair, GM stem cell therapy, and xenotransplantation of genetically modified animal cells (but not solid organs).

11. GTAC *does not* normally wish to consider any study which may be deemed to fall within the general definition, but which is adequately reviewed by other national or local ethics committees. Such research includes, for example:

- transplantation or transfusion of organs or cells, from whatever human source, provided that they have not been genetically modified;
- xenotransplantation of solid animal organs;
- vaccine studies, involving the use of genetically attenuated viruses intended to raise a prophylactic immune response to that virus (provided that the virus does not express any heterologous proteins);
- *ex vivo* fusion of autologous cells and other cells, for example dendritic cells, for the treatment of cancer.

12. In cases of doubt, researchers are invited to contact the GTAC Secretariat for an informal discussion prior to submitting a research proposal.

Germ line gene therapy

13. In line with the Clothier committee report and relevant international Instruments, research aimed at modifying the Germline of subjects will not be considered at this stage. The possibility of inadvertent targeting or modification of germ cells should be carefully assessed during pre-clinical studies. GTAC will need to be satisfied that measures are in place to ensure that patients do not conceive a child during or shortly after the study.

Relationship between GTAC and other agencies

Local Research Ethics Committees

14. Any proposal to carry out gene therapy research on human subjects must comply with the established system of review by a local research ethics committee (LREC). LRECs must be consulted about any research proposal involving NHS patients, their records or NHS premises. A new web-site containing details of LRECs will be launched shortly: http://www.doh.gov.uk/research/recs.

15. Where a research project is to be carried out within five or more LRECs' geographical boundaries and hence would normally be referred to a multi-centre research ethics committee (MREC), GTAC acts as the MREC for gene therapy research.

16. The timing of LREC reviews will vary depending on the local arrangements and on the nature of the research. Researchers are advised for reasons of practicality to submit applications to GTAC in advance of the LREC.

Medicines Control Agency

17. The MCA is required by legislation to assess the safety and quality of medicinal products to be used in clinical trials. Before testing gene therapy products in patients, sponsors or investigators must apply to the Medicines Control Agency for a Clinical Trial Certificate (CTC), a Clinical Trial Exemption (CTX), or a Doctors and Dentists Exemption (DDX), or claim the "named-patient" exemption in writing.

18. Further details of MCA's role in regulating gene therapy medicinal products can by obtained by contacting the MCA Clinical Trials Unit (Tel: 020 7273 0327) and be found at: http://www.open.gov.uk/mca/mcahome.htm

Medical Devices Agency

19. Some forms of gene therapy may involve the use of medical devices, for example novel delivery systems. Details of the regulation of medical devices and the role of the MDA can be found at: http://www.medical-devices.gov.uk/

UK Xenotransplantation Regulatory Authority (UKXIRA)

20. UKXIRA is responsible for approving proposals to conduct xenotransplantation on human subjects. If a gene therapy proposal involves the transfer of viable animal tissue to patients, the GTAC Secretariat will discuss with the UKXIRA Secretariat how to consider the application. In some cases UKXIRA will consider a proposal in parallel with GTAC. The xenotransplantation process would require UKXIRA to make a recommendation to UK Government Ministers who would then make the final decision. Further information can be found at: http://www.doh.gov.uk/ukxira.htm

Genetically Modified Organisms Regulations

21. Proposals to conduct gene therapy research, where they involve the use of live genetically modified organisms (for example, a genetically modified viral vector delivery system), must comply with the relevant regulations controlling the contained use or deliberate release of genetically modified organisms. These are concerned with the protection of human health and the environment. Contained use is where control measures are used to limit contact of the GMOs with people and the environment. Where contact cannot be appropriately limited the activity is likely to constitute a deliberate release.

22. Further details on contained use legislation may be found in, "A guide to the Genetically Modified Organisms (Contained Use) Regulations 1992", as amended in 1996 (ISBN 0-7176-1186-8). This Guide will be replaced by " A guide to Genetically Modified Organisms (Contained Use) Regulations 2000" once expected new legislation has been produced (ISBN 0-7176-1758-0). Detailed technical guidance in matters such as risk assessment and containment measures can be found in the Advisory Committee on Genetic Modification's Compendium of Guidance which is available on the HSE web site: http://www.hse.gov.uk/ .

23. For further advice about contained use legislation and technical guidance contact the Health and Safety Executive, GM Notifications Unit, Technology Division 6, Magdalen House, Stanley Precinct, Bootle, Merseyside, L20 3QZ. Tel: 0151 951 4722, Fax: 0151 951 3474.

24. For further details on deliberate release legislation contact the Department of Environment, Transport and the Regions: http://www.detr.gov.uk/

Method of working

25. In order to develop experience of the issues raised by gene therapy, GTAC has previously sought comments from external reviewers and held discussions with the proposers in full committee. However, increasing experience of gene therapy proposals allows a case-by-case approach to the review process.

26. GTAC therefore intends to move towards a more graded system of review, based on the novelty and complexity of the proposal and the extent to which it clearly falls within GTAC's remit.

27. In general, full GTAC review will be appropriate for studies that involve novel delivery systems, that extend the use of known agents to a different disease, raise new ethical issues, pose significant risks to subject's health or raise wider safety issues for the patient, staff or public health or are proposed by groups with no prior experience of clinical gene therapy research.

28. In all cases it is recommended that those contemplating gene therapy research submit a completed GTAC application form at an early stage. The Secretariat will then be in a position to provide informal advice on the need for a full GTAC application and the likely route of review.

Decisions of the committee

29. The outcome of the above review process will be sent to the lead applicant, the LREC, the host institution and the MCA. This might take the form of unconditional approval; conditional approval; deferral with recommendations for changes before the proposal is reconsidered or rejection. In all cases where further information is sought, the Committee will give its reasons to the applicants in writing and encourage dialogue via the Secretariat.

Disclosure of information

30. Applications to GTAC will be considered to be in confidence and treated as such throughout the review process, including the external review stage. However, care should be taken to ensure that information that might serve to identify individual patients or groups of patients is not included. This is particularly relevant to studies that involve rare diseases or small patient groups.

31. Some elements of a proposal may be considered to be commercially confidential. Such information should be clearly marked and supported by a reasoned justification for the claim. This will enable the Secretariat to determine how to handle the proposal during review. It should be stressed that failure to provide sufficient information at the initial stages will inevitably lead to delay in the GTAC review process.

32. A summary of the discussions at GTAC is placed in the public domain after each meeting. This is normally via a summary of the meeting posted to the GTAC web pages (www.doh.gov.uk/genetics/gtac.htm).

Reporting requirements

Adverse Event Reporting

33. Researchers are required by law to report all serious unexpected adverse reactions[1] (SARs) in gene therapy studies to the MCA in accordance with their requirements. In addition all serious adverse events[2] (SAE) should be reported to GTAC within 14 days (7 for death) regardless of whether the event is deemed related or unrelated to the gene therapy and whether unexpected or expected. In the case of a subject's death, a more detailed report, including, where appropriate, findings at post mortem, additional studies and a statement on the cause of death should be submitted as soon as possible.

34. Summaries of all Adverse Events should be reported to GTAC on an annual basis as part of the annual progress report (see paragraph 40). Adverse events should also be notified to the relevant LREC in accordance with their requirements.

35. The report should use the standard format for reporting adverse reactions to medicinal products, however GTAC's reporting arrangements are in addition to those for reporting severe adverse reactions to the MCA.

Long term flagging project

36. GTAC has advised that there should be arrangements for the long-term monitoring of the subject and for monitoring any subsequent children born to those who have taken part in gene therapy research. This will in future be possible via the GTAC Flagging Project involving the NHS Central Registry and the Office of National Statistics (for those living in England and Wales) or the General Register Office for Scotland (for those living in Scotland). This study has been approved by an independent MREC.

37. Proposers are asked to seek informed consent from all subjects capable of giving it (or otherwise on behalf of the subject) at the time of their enrolment for monitoring of their long-term health and on behalf of any children that the patient may conceive following participation in the study.

38. For the purposes of clinical audit, subject's NHS records will be flagged indicating that they have taken part in a gene therapy research study. Investigators will be asked to provide directly to the Office for National Statistics (or General Register Office for Scotland) the NHS numbers of each subject along with a cipher specific to the study and one to identify the subject within that study. Submissions to the ONS will be on a six-monthly basis using the supplied electronic pro-forma for the purpose of emailing returns.

39. Clinical records and specimens from gene therapy patients should be stored indefinitely to enable follow-up. The storage of DNA samples needs special consideration and appropriate consent.

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[1] A serious noxious and unintended response to a medicinal product.

[2] A serious untoward medical occurrence which does not necessarily have to have a casual relationship to the medicinal product.

Progress reports

40. All investigators with active studies will be asked to provide an annual progress report to GTAC. A format for this will be supplied by the Secretariat each year, covering matters such as progress with the recruitment of subjects, observed adverse events and any relevant clinical findings. These progress reports will not be released by GTAC, however, the data provided, for example on the total number of gene therapy patients, may be incorporated into the GTAC annual report. No information will be released that may identify individual patients.

41. GTAC also expect to see reports on completion of the study and would encourage prompt publication in peer-reviewed journals as a means of promoting wider dissemination of research findings.

Information to be included in GTAC applications

GTAC must be given sufficient information to make a judgement about the ethical acceptability of the study.

Proposals for gene therapy research submitted to GTAC should normally consist of:

- ✔ A GTAC application form;
- ✔ The clinical protocol;
- ✔ Patient information material and consent forms;
- ✔ Information about relevant qualifications and experience of the principal investigator(s);
- ✔ Details supporting the suitability of the research centre.
- ✔ Supporting technical appendices.

42. GTAC has developed an application form to provide a common framework for an overview of the design of the study and the issues that it raises. The application form is available on the web, by email from the Secretariat or as a hard copy.

43. For full proposals, the clinical protocol and a succinct summary of relevant pre-clinical and safety data (possibly including that prepared for other regulatory bodies) should support the application form.

44. Proposers should aim to strike a balance between giving sufficient information to enable the committee and external referees to understand the study whilst keeping the documents accessible to the lay members of the committee.

45. The following headings are suggested to structure the proposal. In some cases the information may be adequately conveyed in the study protocol, in others it may be necessary to provide additional supporting information in the application form or technical appendices.

A. Objectives and rationale

46. There should be a brief introductory statement that provides the background to the proposed research. It should refer to the disease to which the study relates, its prevalence, severity and health burden; their natural history and biology; the available therapies, what is to be learnt from the research and the potential for improving the subject's health.

B. Patient population

47. The proposal should describe and justify the proposed study population, bearing in mind GTAC's key principles (paragraph 8).

Risk/benefit

48. The proposal should include an appraisal of the risks to the subject and the possible benefits. This should include a summary of the alterations to normal clinical care that will arise as part of the research, especially any invasive procedures and those that may be uncomfortable or inconvenient for the subject (such as procedures that involve lengthy or frequent attendance as outpatients or in-patients or requirements to remain in an isolation room).

49. The patient's disease should also be relatively stable with a predictable likely clinical progression. In cases where there is rapid progression, GTAC will need to be convinced that the clinical management of the patient will not be impaired by the requirements of the trial.

C. The gene construct and delivery system

50. The proposal must include details of the genetic material and its manufacture to enable an assessment of the safety and likely benefit. Technical information such as sequence data, derivation of vectors and producer cell lines may be provided as part of the supporting technical appendices.

51. The proposal should describe the nature and structure of the genetic material that is to be administered and the rationale for its use. It should include:

- an overview of the therapeutic gene construct and its regulatory elements;
- the methods used to produce it, including any producer cell lines;
- the method of delivery, and;
- the form in which the material will be administered to the patient.

Manufacture

52. The proposal should summarise the arrangements for the manufacture and handling of the therapeutic product. The detailed arrangements for achieving compliance with the requirements of the MCA are not normally required, but may be appended as part of the supporting technical material.

D. Prior studies

53. The proposal should describe the evidence relating to the safety and likely efficacy of the proposed gene construct and delivery system. Wherever possible the data presented should relate to the proposed construct and delivery system in the most appropriate *in vitro* or animal model of the disease. Where this is not possible there must be a full account of how the data is extrapolated to the intended disease and construct. In some cases available data may also be extrapolated to avoid excessive animal studies, especially in non-human primates.

54. The proposal should provide a reasoned justification for the choice of construct and delivery system. In particular, GTAC will be looking for evidence that the safety of the proposed study has been considered in depth at the pre-clinical and clinical stages. This should include consideration of the stability of safety features in any viral vectors used and tests to assess the presence of contaminants.

55. Where possible, reference should be made to any previous applications to GTAC, to published studies and to guidance from GTAC or others on the safety and tolerance of the vector system in human subjects.

Pre-clinical studies

56. The evidence provided from pre-clinical studies should normally include:

- Studies of the gene delivery system;
- Studies demonstrating gene transfer and expression and biological effect;
- Studies to demonstrate target specificity;
- Studies relating to the route of entry;
- Studies related to the safety of the genetic material and the delivery system. In some cases this may be supported by material elsewhere in the proposal, such as on the delivery system and manufacture.

Distribution to non-target organs

57. The proposal should provide evidence of the target specificity of the therapeutic product and, where appropriate, the absence of accumulation/retention on non-target tissues or organs, especially the gonads.

Previous clinical experience

58. A summary of relevant data from previous clinical trials, including peer-reviewed publications, should be submitted to support the safety and likely efficacy of the proposed study.

E. Study protocol

59. The detailed arrangements for the clinical and technical procedures involved in the research should be specified in the study protocol. This should include an outline of the clinical procedures and the tests used to monitor the patient.

Study design

60. The type of study being proposed, the size of the study population and other relevant factors should be detailed. There should be some consideration of whether the procedures and requirements are reasonable and equitable.

Criteria for inclusion/exclusion

61. The inclusion and eligibility criteria should be detailed. The number of subjects should be given, along with a comment on the likelihood of recruiting sufficient subjects. There must be careful characterisation of the specific patient population for the studies regarding not only their disease, its stage, and previous standard treatments, but also the expected prognosis.

62. The proposal should set out what other options would be available to such patients in clinical practice or current clinical research. Specific inclusion and exclusion criteria by virtue of disease, abnormal tests or treatment, should be justified explicitly in relation to the treatment and/or its evaluation.

63. Where subjects are to be HIV tested for the purpose of excluding HIV positive patients from the gene therapy study, consent for the test should be explicitly sought and the appropriate provision made for counselling.

64. The eligibility criteria should take account of the need to minimise the risk of unintended transfer of genetic material to germ cells or the fetus. If conception is possible, it should normally be a condition that subjects or their partners use an effective form of birth control during and for at least 3 months after the study. Fertile women should have a negative pregnancy test shortly before commencing the study.

65. Children should be the subject of research only when it is essential and the information could not be obtained from adult subjects or in any other way. Where children are to be the subjects of such research, then the presumption must normally be that there is some possibility of therapeutic benefit for the child. The child's parents or legal guardian must be fully informed and consent obtained. The minimum age for entry into an adult trials should be set at 18 years.

Dose escalation studies

66. Particular attention should be given to the design of dose escalation studies to ensure that early indications of dose limiting toxicity can be identified. Investigators should set the initial dose to be administered to patients at least two logs lower than the maximum safe dose predicted by pre-clinical studies.

67. GTAC will normally wish to see details of the arrangement for assessing toxicity and considering progression to the next dose level. This might include details of the parameters to be used in assessing adverse effects and toxicity. Where there is a reference to standard criteria, e.g. the NCIC toxicity criteria, it is not necessary to reproduce these in full.

68. For certain protocols raising particular safety issues, GTAC may wish to be provided with safety data for each dose level before giving permission to proceed to a higher dose. A case-by-case assessment will be made by GTAC when reviewing proposals to determine whether investigators should seek approval for progression between doses. No unnecessary delay in granting approval for to proceed to the next dose level is anticipated.

69. In any Phase I study, no further patients should be dosed following an unexpected, clinically meaningful grade IV toxicity until the investigator has adequately reviewed the monitoring and safety data. Procedures for review in this event should be detailed in the protocol. Any necessary amendments to the protocol and patient information material should be approved by GTAC before the trial recommences.

Additional clinical procedures

70. The protocol should detail the clinical procedures, particularly those that are in addition to or differ from normal patient care. This should include details of any preliminary treatments, for example surgery or chemotherapy to remove or reduce the number of abnormal cells.

71. The procedures and regime for administering the gene therapy material should be given, including the nature and timing of administration and monitoring.

72. If cells are to be removed and treated *ex-vivo* details should be provided of the type of cells and the procedures to be used.

Monitoring

73. Screening tests used solely for the purpose of the study should be explained and justified. Arrangements should be set out for explaining to patients, and performing those that are not part of standard care, but which result from participation in the study.

74. The arrangements for monitoring subjects before and after the administration of the genetic material should be given. It should specify the frequency and duration of monitoring, the biochemical, physiological, pathological tests to be done, the clinical endpoints of the study and whether special post-mortem studies will be requested if a patient dies.

75. The monitoring procedures should be designed with a view to identifying at an early stage the possible side effects so that action can be taken to prevent or mitigate such events. The relevance of tests used in monitoring the study should be set out, together with sufficient detail on those that are not standard practice to enable their assessment. The way in which such tests are to be analysed in relation to study end-point should be made clear, including the validation of novel techniques where appropriate. If material is to be stored and/or transported long distances, evidence should be provided to show that the process of storage and/or transport and any consequential delay, do not adversely or unpredictably affect the results obtained.

76. There should also be some consideration of the methods used to determine whether the gene sequences are inserted and expressed in the subjects. This might include, where available, tests to determine any non-target effects, such as expression in other tissues or cells or shedding of vector into the wider environment.

77. A reference sample of the material injected should be stored to allow for retrospective analysis. Where possible, it is also recommended that serum (and, if feasible, cell) samples should be taken at suitable intervals and stored to provide for retrospective analysis in the event of adverse reactions.

78. GTAC has prepared separate guidance on monitoring of studies involving adenovirus vectors (see references).

F. Information for patients and consent

Patient Information Leaflets

79. The application should detail the arrangements for informing prospective subjects, or their parents or guardians in the case of children, about the research before seeking consent to take part in the study. The application to GTAC will need to include copies of the patient information sheet that subjects will receive, as well as any wider promotional material about the research team or unit (including any material available on the Internet) if this mentions gene therapy.

80. There should be a simple introductory document that explains, in non-technical language, what is proposed. This should be supported by arrangements for further oral and/or written information. Advice on preparing clear patient information material is at Annex 1.

81. GTAC is sensitive to the hopes and motives of potential participants who have a life-threatening disease, and it is imperative that they understand clearly when a trial offers them no prospect of clinical benefit. It is also important to make clear whether or not participation in the initial non-therapeutic stages of a research programme influences their eligibility for future therapeutic studies.

82. GTAC also advocates appropriate independent counselling for research subjects, and details of the arrangements should be clear from the proposal and the patient information leaflet.

Consent

83. Research subjects should take part in gene therapy research trials only after a full explanation of the procedures, risks and benefits and after they have given their consent, if they are capable of doing so.

84. Consent should also be sought for each participant's NHS number, in an anonymised form, to be sent to GTAC and to be recorded on the central NHS register. In order to obtain consent to the flagging arrangements, two standard paragraphs should be inserted into the patient information leaflet (see Annex I).

Insurance

85. The proposal should confirm that appropriate insurance or indemnities are in place to cover the participants in the trial.

Payments

86. Subjects should have their travel and other out of pocket expenses fully reimbursed. The patient information sheet should make clear that they will not be expected to meet the costs of any clinical procedures (material, tests or medical care) related to the study.

G. Details of Investigator(s) and nature of the research site

87. GTAC wishes to be satisfied that gene therapy is only conducted in centres of excellence, until it can be considered to be a normal part of clinical research. Therefore, the proposal should provide details of the staff (especially the Principal Investigator) and the facilities in which the research will take place (the Host Institution). In particular this information should demonstrate that there is:

- a substantial multidisciplinary team of clinical researchers,
- a suitable infrastructure of facilities in clinical and laboratory environments,
- on-site support in a range of disciplines, including microbiology/infection control, immunology, and;
- a proven track record of high-grade clinical research.

88. The proposal should be supported by a summary of the relevant training and experience (in the form of a brief CV) of the principal investigator (PI). The names and qualifications of junior clinical and research staff should also be provided. There should be appropriate arrangements to ensure adequate supervision of junior staff and access for the patients to the PI in the event of problems or queries.

89. Arrangements should be in place to ensure that there is no untoward conflict of interest, financial or otherwise, between the trial sponsor and those individuals responsible for enrolling and caring for the patients.

90. It is strongly recommended that the proposal identifies an individual with day-to-day responsibility for overall co-ordination, including liaison with GTAC. This might not be the same person as the PI, recognising that such people are often involved in a number of trials and other activities.

Containment

91. The arrangements to safeguard people other than the research subject, including clinical and non-clinical staff, relatives and visitors and the wider public will normally form part of requirements of the Health and Safety Executive. The GTAC proposal should, however, include information on the anticipated hazards of the proposed research and the proposed control measures. In particular it should highlight any measures over and above those required for normal clinical care, such as keeping the subject in isolation during the study, handling of any dressing and any restrictions on visitors.

ANNEX 1 – WRITING INFORMATION LEAFLETS FOR THOSE PARTICIPATING IN GENE THERAPY RESEARCH

92. The following section is based on guidance first issued in 1995. It provides more detailed advice for those with clinical responsibility for participants and those with responsibility for the design of gene therapy trials.

93. This guidance should be read with the sources of general advice on patient information and consent (see Bibliography).

Informing Patients

94. Enabling the potential subjects of research to make a decision whether or not they might participate is one of the most important aspects of the ethical acceptability of research. They must be well informed about the procedures and risks of the protocol and the responsibilities that they are being asked to take on. This is true of all medical research which involves human subjects, but is especially so in the field of gene therapy. Not only is the topic unusually complex, but there is likely to be a need for long term follow up.

95. Although information can be given in a number of ways, the written information leaflet is particularly important and should always be provided. It is a permanent record of the key points of any research trial, to which the patient can refer, and therefore a critical element in informing consent. The document also provides a source of reference for families and friends. In addition it gives both Local Research Ethics Committees (LREC's) and GTAC an opportunity to assess this aspect of the research protocol.

General Principles

96. There is no single correct way of writing information for patients. The aim must be to present sufficient but not excessive information in a form that is understandable. This calls for thoughtful and tested use of language, vocabulary and presentational techniques.

97. Understanding, and recall, of what to many patients will seem to be complex information, are reduced by:

- anxiety
- poor presentation
- complex language, technical terms and jargon.

98. Conversely, understanding and recall are enhanced by:

- keeping the format simple, so that it can be read and re-read at leisure;
- use of plain English;
- ensuring that other modes of communication, such as counselling, reinforce and amplify the written information, but do not contradict it.

99. Patients must be encouraged to ask questions about the research. Time must be set aside for the investigator to go over the information with patients to ensure that they understand all the implications. Patients will often only remember important questions after the first counselling.

100. The advice contained in this guidance covers three aspects of preparing information leaflets:

- The information to be included
- How to present the information
- How to evaluate its effectiveness

What to Include

101. It is important to anticipate common concerns. Below are listed some common questions.

- Why have I been chosen for the study?
- Is the treatment really likely to cure me or not? The answer should be unambiguous.
- There should be no false hope.
- Are there any risks or disadvantages for me?
- What will the treatment entail? How, when, where and how often will it be administered and monitored?

- What will the side effects be? Will it be painful or uncomfortable?
- What costs or inconveniences may I incur?
- What are the responsibilities placed upon me for follow-up?
- What will the trial help to demonstrate?
- What action should be taken if I become unwell?
- Who can I talk to about this study?

102. The following points should be covered in addressing these concerns.

Why the research programme is being undertaken

103. Explain the purpose of the study. This needs to cover:

a. The research questions being asked:

- Why are they important?
- How might they be answered?
- Why has gene manipulation been chosen?
- How the study has been designed:
- Increasing dosage. Why is this necessary?
- Use of placebo controls and what this means.
- Does the study involve more than one centre?
- Evaluation of results.

b. The implications of the research for the individual.

Research procedures

104. Describe and explain the procedure(s) and commitment of participants in terms of time, costs, and how data will be collected (such as blood tests, x-rays, interviews). Describe any restrictions the research might place on the patient, particularly the use of isolation rooms and restrictions on visiting.

Consequences of participating

105. The predictable consequences of participating in the study should be explained.

a. State whether or not there are possible benefits of participating in the proposed study. For research trials which are not reasonably expected to provide a therapeutic benefit to participating patients the information leaflet should clearly state that no direct clinical benefit is expected to occur as a result of participation in the study, although knowledge may be gained that may benefit others.

b. Describe the nature and likelihood of risks, pain, injury or other harm, that may occur.

c. Where it is appropriate to the patient, describe alternative therapies, including those being assessed in other research trials.

Non-participation or withdrawal from the study

106. Emphasise that participation in any study is voluntary. The decision to take part or not, should not influence any present or future treatment or care. Patients should know that they can withdraw from the study at any time without having to give a reason for doing so. Draw attention to any additional risks that might be associated with an incomplete course of treatment.

Use of contraception

107. It is important to avoid the possibility that any of the reagents used in gene transfer research could harm a fetus. Advise women that they should not become pregnant before or during the course of their participation in the study. Inform both men and women when effective contraception or abstinence is required during the active phase of their participation in the study and also for at least 3 months afterwards. Depending upon the nature of the research trial the information sheet might advise any woman not to participate if she thinks she may wish to become pregnant.

Confidentiality/ Privacy

108. Affirm that confidentiality of personal information of trial participants will be protected. State who might have access to their anonymised research records and why this is necessary. In trials where personalised data needs to be reviewed, the patient's agreement must be obtained and this aspect of the research should be clearly explored in the information leaflet.

Long term follow-up

109. It is important to evaluate the long term safety and efficacy of gene transfer. This requires co-operation of participants in follow-up beyond the active phase of the study. Explain the need for this commitment from the outset. The information leaflet or consent form should include a list of persons who can be contacted during the follow-up period.

110. Patients participating in gene therapy studies will be subject to clinical audit via the NHS central records system. In addition they will be invited to participate in the GTAC Flagging Project involving the NHS Central Registry and the Office of National Statistics. Proposers are asked to seek informed consent from all subjects at the time of their enrolment for monitoring of their long-term health and on behalf of any children that the patient may conceive following participation in the study.

111. The following paragraphs should be inserted into the patient information leaflet.

"Gene Therapy is a new development. Every effort is made to be sure it is safe but we need to watch out for any unexpected effects. To make this possible, all people who have gene therapy are flagged by the NHS records system. Accordingly, your NHS number and details of the trial in which you are participating will be provided to the Department of Health (DH) so that your participation in this trial can be recorded on the National Health Service Central Register. This information will be used for purposes of long-term follow-up. You will not be contacted by DH directly but your GP may be asked to provide information on your health on occasion.

In theory, gene therapy could affect the next generation. To cover this possibility, any children born to a person who had gene therapy will be flagged also and followed through until they are 16 years old. This system is subject to the same protection of confidentiality as all medical records. Any studies of these medical records will be under the supervision of the Gene Therapy Advisory Committee of the Department of Health who will make sure confidentiality is respected."

Further support

112. The information leaflet should make clear to potential participants who can be approached for:

a. further information

b. counselling.

How to write it

113. Experience has shown that it is best to:

- keep sentences short
- make only one point in each sentence
- use simple words
- avoid technical terms whenever possible. When they cannot be avoided, explain what the terms mean in simple language
- repeat important points in different ways
- avoid crowding pages with too much information
- summarise the key points.

Evaluation of a Patient Information Leaflet

114. To determine how well an information leaflet will be understood it needs to be evaluated. Asking people not acquainted with the area to read the leaflet is the best way. They might include administrative or clerical staff in the hospital, or non-medical friends. The management of your hospital may be able to assist in "piloting" the leaflet. Patient groups and other voluntary organisations are an important source of advice on both design and piloting leaflets.

115. The two most common ways in which written information is evaluated formally involve using readability formulae and through formal assessments by patients.

116. The "readability" of any text can be estimated by the application of standard formulae. Most modern word processing software can derive these figures automatically. The table below gives an interpretation of the Flesch reading ease score. A reading ease score for patient information leaflets of between 80 and 90 is desirable.

Reading ease	Verbal description	Typical text	Estimated Percentage who would understand
90-100	Very easy	Comics	97
80-90	Easy	Tabloids	95
70-80	Fairly easy	Popular	90
60-70	Standard	Magazine	90
50-60	Fairly hard	Broadsheet	77
30-50	Difficult	Academic	31
0-30	Very hard	Scientific	7

117. Assessments of leaflets by patients might include measures of understanding and satisfaction with the information provided.

Special Issues

118. Potential subjects need time to make a decision about their participation in the research. They should have an opportunity to consider the information provided, seek further information and to consult with a named independent counsellor.

119. Where the study involves children who are not capable of giving consent, an information sheet for parents or guardians should be prepared according to the principles above. In addition, information should be provided to the child which is appropriate to the understanding ability of that child

120. Additional consideration should be given to the needs and requirements of subjects whose first language is not English. The importance of written information is often greater in such circumstances. Special care should be taken to have information leaflets in other languages checked for accuracy, and to ensure cultural and ethnic sensitivities are properly handled.

121. Every effort should also be made to ensure that individuals who have difficulty reading are not disadvantaged through lack of information.

Further reading

[1] NHS Management Executive. "A guide to consent for examination or treatment" 1990 Department of Health. This is currently being updated.

[2] Scottish Office "A guide to consent for examination or treatment" Scottish Office Home And Health Department

[3] Royal College of Physicians."Research involving patients". London: Royal College of Physicians. 1990.

[4] Consumers for Ethics In Research. "Spreading the word on research or patient information: how can we get it better?" CERES. 1993 (This is a very practical guide to drafting patient information with excellent examples on both good and bad practice. This can be obtained from: CERES, PO Box 1365, London N16 0BW).

[5] Flesch, R. (1948) "A new readability yardstick." Journal of Applied Psychology 32: 221-33.

SECTION 2 – REPORT OF THE ADENOVIRUS WORKING PARTY

INTRODUCTION

1. The Gene Therapy Advisory Committee (GTAC), established by Government in 1993. oversees the conduct of gene therapy in the United Kingdom. GTAC approval must be obtained before somatic gene therapy or gene transfer research is conducted on human subjects. The primary concern of GTAC is the ethical acceptability of each research proposal and GTAC review places emphasis on the need to ensure the safety of the subjects of research.

2. This document is intended as a supplement to the GTAC's General Guidance Notes[1], and should be consulted when proposals are made to conduct adenoviral gene therapy in the United Kingdom.

3. In Spring 1999 GTAC began a review of serious adverse events (SAEs) reporting and issues related to the monitoring of gene therapy patients. As events unfolded in the USA in relation to the death of a patient enrolled for Gene Therapy in an adenoviral study, the GTAC review was concentrated on UK adenovirus studies. At the time of the initial survey, 69 patients all with advanced cancer, had been recruited into 11 adenoviral gene therapy research protocols.

4. GTAC subsequently agreed to conduct a more detailed review of UK studies and to convene an ad hoc adenovirus working group whose membership was drawn from the GTAC, other regulatory bodies and the research community. The latter survey confirmed that no major life-threatening toxicity had occurred in relation to the use of adenoviruses in the UK.

5. The working group met in London, on 11 April 2000 with the following remit:

   - To review current UK practice in adenoviral gene therapy clinical trials, including adverse event reporting.
   - To establish recommendations in relation to GTAC's guidance with respect to adenoviral gene therapy clinical trials.

6. The following supplement to GTAC's Guidance Notes is issued in accordance with the recommendations of the Working Party and approved by GTAC. The recommendations are based on such factual information as received regarding the adenovirus-related death of the patient in the USA. Specific recommendations on monitoring reflect these considerations, and suggest practicable and generally available measures to address these. The need to issue further recommendations, in the light of receipt of substantive additional information will be kept under review.

SUMMARY OF MAIN CONCLUSIONS AND RECOMMENDATIONS OF THE WORKING PARTY

Patient surveillance and monitoring

7. The level of monitoring recommended by the working party reflects concerns related to risks associated with the route of administration, particularly those related to systemic exposure to the vector.

8. In addition, for dose escalation studies, it is recommended that patients be closely monitored for early signs of toxicity. Such signs, which may not be severe, may indicate that the dose levels are approaching a maximum tolerated dose under which circumstances investigators should reduce the increments between future doses.

9. Clinical monitoring that is part of routine monitoring (eg: blood pressure, temperature, respiratory rate and so on) should be carried out at least quarter-hourly for the first hour, hourly till 6 hours, then six hourly for 24-48 hours. In addition to routine monitoring the following additional investigations are recommended as a minimum:

   - Measurement of anti-adenovirus antibody, both pre- and post-dosing.
   - Pre-treatment assessment of T cell population – CD3/CD4/CD8. Whether or not conducted prospectively, it is recommended that samples be sorted to allow for retrospective analysis in the event of a serious adverse reaction.

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[1] GENE THERAPY ADVISORY COMMITTEE (2000). *Guidance on Making Proposals to Conduct Gene Therapy Research on Human Subjects* (Department of Health, London).

Further, the storage of serum (and, if possible, cell) samples at suitable intervals (including pre-administration) is strongly encouraged to provide for retrospective analysis in the event of adverse reactions. Where possible, a reference sample of the material injected should be stored to allow for retrospective analysis.

10. For intra-vascular administration, it is recommended that investigators routinely measure (with rapid turn-around for results) the following investigations, as close as practicable to the start of treatment and daily in the first 3-4 days post-treatment, and longer if they show abnormalities:

- Full blood count with white cell and platelet count (6-8 hourly for the first 24 hours).
- C-Reactive Protein (6-8 hourly for the first 24 hours).
- Complement C3 and, if possible, C3 breakdown products.
- Coagulation studies.
- Fibrinogen.
- Fibrin split products.
- Liver enzymes: AST/ALT/ALP.
- Gamma Glutamyl Transpeptidase (GGT).
- Bilirubin.
- Creatinine, Urea and Electrolytes.
- Urine microscopy.
- Proteinuria.

The working party further recommend that researchers consider monitoring:

- Serum cytokines (eg IL-6/IL-10/TNF-α).

11. Whether or not conducted positively, it is recommended that serum be stored to allow for retrospective analysis in the case of severe adverse reactions.

12. The results of pre-treatment assessments should be known before treatment commences.

Intra-hepatic Arterial Administration

13. Administration of adenovirus by the intra-hepatic artery route was considered to present a greater theoretical risk to the patient than the intra-tumoural route. Additional considerations will be applied by GTAC in reviewing studies utilising this route. The committee will need to be satisfied that use of the intra-hepatic arterial route is fully justified.

14. Researchers proposing to administer adenovirus by the intra-hepatic artery route should implement extensive patient monitoring and this should be performed on an in-patient basis. GTAC will require reassurance that all patient monitoring data and safety data has been considered, prior to progression to the next dose level in dose escalation studies.

Standardisation of Dose

15. The need for accurate standardisation of dose was acknowledged. The working party recognised that this was a global issue and would seek to encourage the research community to work towards the development of reference standards for use as controls in assays of vector potency. Until a universal standard has been established, researchers should endeavour to attain comparability in terms of infectious units : particle ratios in any given study or series of studies.

16. Investigators should set the initial dose to be administered to patients at least two logs lower than the maximum safe dose predicted by pre-clinical evaluation of the actual vector to be used by the specific route of administration. If one patient out of three experiences a grade III/IV toxicity at any dose level it is recommended that the cohort be expanded to 6 in order to establish whether the maximum tolerated dose has been reached.

17. For certain protocols raising specific issues, GTAC many wish to be provided with safety data for each dose level before giving permission to proceed to a higher dose. A case by case assessment will be made by GTAC when reviewing proposals to determine whether investigators should seek approval for progression between doses. No unnecessary delay in granting approval to proceed to the next dose level is anticipated.

18. Whilst GTAC approval may be initially granted for half or whole log increments, investigators are encouraged to reduce these increments at high doses, where patient monitoring is predictive of marked toxicity at the next planned dose. GTAC approval should be sought for any change to dose escalation increments and the relevant patient monitoring data submitted for consideration.

19. No further patients should be dosed in an ongoing study following an unexpected clinically meaningful grade IV toxicity until the monitoring and safety data have been adequately reviewed by the investigator. Suitable amendments to the protocol, designed to minimise risk to future patients and to inform patients of any additional risks, should be submitted to, and approved by, GTAC before the trial recommences.

Appropriateness of Patient Group

20. To date, all patients enrolled in UK adenoviral gene therapy clinical trials have had advanced cancers. Whilst the choice of patient group should reflect the stage of the investigation, a case by case assessment will be carried out by GTAC with regard to patient group suitability. In reaching a decision, GTAC will carefully consider the potential risks against the possible benefits. It is recommended that only patients whose disease is severe or life-threatening should be recruited into dose escalation studies.

21. The patient's disease should also be relatively stable with a predictable likely clinical progression. In cases where there is rapid progression of the disease, GTAC will need to be convinced that the clinical management of the patient will not be impaired by the requirements of the trial.

Reporting of Serious Adverse Events and Reactions

22. A serious adverse event or drug reaction is defined as any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.
- Requires in-patient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.

23. Researchers are required by law to report all serious unexpected adverse reactions (SAR[2]) in gene therapy studies to the MCA in accordance with their regulations. In addition (in requirements for all gene therapy studies) any serious adverse event (SAE[3]), expected or unexpected and whether deemed related to the study product or not, should be reported to GTAC within 14 days (7 days for death). Summaries of adverse events should be reported to GTAC on an annual basis. SAEs should be notified to the relevant LREC in accordance with their requirements.

24. Investigators are strongly encouraged to include in their annual reports to GTAC any monitoring data which is suggestive of a dose-related toxicity but which do not result in clinical adverse events in patients. Such data might assist in the design of future studies by other researchers.

25. In addition, GTAC would value notification of SAEs in studies conducted outside the UK, which may have implications for the safety of patients enrolled in UK studies.

Public Awareness and Sharing of Information

26. A key recommendation of the working party was that any data considered by GTAC to be relevant to patient safety should be provided to other UK adenoviral gene therapy researchers, thereby permitting informed amendment of existing studies. Such sharing of information will be by agreement with the submitting investigator and will have all proprietary or confidential information erased.

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[2] Definition of SAR: A serious noxious and unintended response to a medicinal product.

[3] Definition of SAE: A serious untoward medical occurrence which does not necessarily have to have a causal relationship to the medicinal product.

WORKING PARTY MEMBERSHIP

Professor Alisdair M Breckenridge
Chair of Committee on Safety of Medicines.

Dr Brian Davis
Medicines Control Agency

Professor Anthony Dayan*
Emeritus Professor of Toxicology
University of London

Dr Martin Gore[†]
The Royal Marsden

Dr Peter Harris
Cobra Therapeutics

Professor Stanley Kaye[†]
CRC Department of Medical Oncology
The Beatson

Dr Paul Logan
Health and Safety Executive

Professor Pedro Lowenstein[†]
University of Manchester

Dr Vivien Mautner
University of Birmingham

Professor Norman C Nevin*
(Chairman)
Belfast City Hospital

Professor Anthony Pinching*
St Bartholomew's & the Royal London School of Medicine and Dentistry
Queen Mary & Westfield College

Dr Peter Searle
CRC Institute for Cancer Studies
Birmingham

Dr R Spiegel, SR
VP Medical Affairs
Chief Medical Officer
Schering Plough Research Institute

Professor C Michael Steel*
School of Biological & Medical Sciences
University of St Andrews

Dr Lincoln Tsang
Medicines Control Agency

* GTAC Members.

[†] Not present at 11 April meeting

ANNEX 1 – GTAC TERMS OF REFERENCE

The terms of reference of the Gene Therapy Advisory Committee (GTAC) are:

(1) To consider and advise on the acceptability of proposals for gene therapy research on human subjects, on ethical grounds, taking account of the scientific merits of the proposals and the potential benefits and risks;

(2) To work with other agencies which have responsibilities in this field including local research ethics committees and agencies which have statutory responsibilities - the Medicines Control Agency, the Health and Safety Executive, and the Department of the Environment;

(3) To provide advice to UK Health Ministers on developments in gene therapy research and their implications.

The Committee will have a responsibility for:

(a) Providing advice for applicants on:

- (i) The content of proposals, including the details of protocols, for gene therapy research on human subjects;
- (ii) The design and conduct of the research;
- (iii) The facilities necessary for the proper conduct of the research;
- (iv) The arrangements necessary for long term surveillance and follow up.

(b) Receiving proposals from doctors who wish to conduct gene therapy research on human subjects, and making an assessment of:

- (i) The clinical status of the subjects;
- (ii) The scientific quality of the proposal;
- (iii) The scientific requirements and technical competence necessary for carrying out gene therapy research effectively and safely;
- (iv) Whether the clinical course of the particular disorder is known sufficiently well for the outcomes of therapy to be assessable;
- (v) Sound information, counselling and advice to be given to the subject (or those acting on behalf of the subject);
- (vi) The potential benefits and risks for the subject of what is proposed.

ANNEX 2 – MEMBERSHIP OF GTAC

Chairman

Professor Norman C Nevin BSc, MD, FFPHM,
FRCPath. FRCPEd, FRCP
The Queen's University of Belfast and
Belfast City Hospital

Members

Professor Elizabeth Anionwu, PhD,
RGN, Dean of Nursing,
Wolfson School of Health Sciences
London

Mrs Rosemary Barnes
Chief Executive, Cystic Fibrosis Trust
Kent

Professor John Burn MD, FRCP
Northern Genetics Service
Royal Victoria Infirmary
Newcastle

Professor Anthony Dayan MD, FRCP, FRCPath,
FFPM, FIBiol
St Bartholomew's & The Royal London School
of Medicine & Dentistry
Department of Toxicology
London

Reverend Dr Keith Denison MA, PhD
The Church in Wales
Diocese of Monmouth

Dr Brenda Gibson FRCP, FRCPath, DFM
Department of Haematology
Hospital for Sick Children
Glasgow

Professor Ian Hart BVSC, MRCVS, PhD,
FRCPath
United Medical & Dentistry Schools
of Guy's and St Thomas' Hospitals
London

Mrs Ann Hunt
Tuberous Sclerosis Association

Professor Patrick Johnston
MD, PhD, FRCP, FRCPI
Department of Oncology
Belfast City Hospital

Professor James Neil BSc, PhD, FRSE
University of Glasgow Veterinary School

Professor Anthony Pinching DPhil, FRCP
St Bartholomew's and The Royal London
School of Medicine & Dentistry
Queen Mary & Westfield College
London

Professor C Michael Steel MB, ChB, PhD, DSc,
FRCP Ed, MRCPath
School of Biological & Medical Sciences
University of St Andrews

Mrs Irene Train RGN, RM, RHV, QIDN
Formerly Director Public Health Nursing
Clwyd Health Authority

New Members from December 1999:

Mr Michael Harrison
Chambers of Peter Andrews QC.

Dr Sohaila Rastan
SmithKline Beecham Pharmaceuticals.

Ms Caroline Benjamin
MacMillan Genetic Associate, Liverpool

Observers

Department of Health:
Dr Elaine Gadd

Medicines Control Agency:
Dr Jenny Sims,
Dr Brian Davis,
Dr Lincoln Tsang,

Secretariat

Dr Mark Bale
Mrs Beryl Keeley
Dr Kerry Knight
Dr Jayne Spink
Mrs Margaret Straughan

ANNEX 3 – REGISTER OF MEMBERS INTEREST

GTAC members have declared the following personal share holdings or funding from the biotechnology/pharmaceutical industry.

Professor Norman C Nevin	None
Professor Elizabeth Anionwu	None
Mrs Rosemary Barnes	Director, Association of Medical Research Charities Non-Executive Director, Greenwich Healthcare Trust Non-Executive Director, Greenwich Building Society (now Portman Building Society)
Professor John Burn	Clinical Advisory, Therexsys PLC
Professor Anthony Dayan	Consultancies: Cantab, Fournier, Introgene, Schering Plough & Therexsys PLC
Reverend Dr Keith Denison	None
Dr Brenda Gibson	None
Professor Ian Hart	None
Mrs Ann Hunt	None
Professor Patrick Johnston	Research grant from Bristol Myers Squibb Consultancy, Eli Lilly
Professor James Neil	Research grant from Intervet International BV Ad hoc consultancy, Q-One Biotech
Professor Anthony Pinching	Infrequent consultancies with Roche, Pharmacia Upjohn, Glaxo Wellcome. Travel Sponsorship from Boehringer Ingelheim and Glaxo Wellcome.
Professor C Michael Steel	None
Mrs Irene Train	None
Mr Michael Harrison	None
Dr Sohaila Rastan	Employee of Smithkline Beecham Pharmaceuticals. Holder of Smithkline Beecham shares & share options.
Ms Caroline Benjamin	None

ANNEX 4 – EXTERNAL EXPERT ADVISERS TO GTAC

During 1999 GTAC sought the views of the following expert advisers:

Professor John Arrand
Paterson Institute for Cancer Research
Manchester.

Dr Keith Channon
The John Radcliffe Hospital, Oxford.

Dr Jean-Marc Collombert
Imperial School of Medicine, London.

Professor F Cotter
St Bartholomew's & Royal London
School of Medicine.

Professor Kay Davies
University of Oxford.

Professor John Goldman
Imperial College of Medicine,
Hammersmith Hospital, London.

Dr R Gopal
Public Health Laboratory Services, Colindale.

Professor Robert Hawkins
Christie CRC Research Centre, Manchester.

Dr Tim Helliwell
University of Liverpool.

Dr Simon J Hollingsworth
The Royal Free & University College
London Medical School.

Dr J A Ledermann
The Royal Free & University
College London Medical School.

Professor Nick Lemoine
ICSM at Hammersmith Hospital, London.

Professor R Leonnard
ICRF Medical Oncology Unit, Edinburgh.

Dr Keith N Leppard
University of Warwick, Coventry.

Professor P Lowenstein
University of Manchester.

Professor D Lowrie
National Institute of Medical Research.

Professor A C Minson
University of Cambridge.

Professor E S Newlands
Imperial College of Science,
Technology & Medicine.

Professor Peter O'Hare
Marie Curie Research Center, Surrey.

Professor M Partridge
Kings College Hospital, London.

Dr Peter Searle
CRC Institute of Cancer Studies, Birmingham.

Dr Richard Thompson
King's College Hospital, London.

Dr Adrian Thrasher
Institute of Child Health, London.

Professor C R Wolf
University of Dundee.

Professor Wynford-Thomas
University of Wales College of Medicine,
Cardiff.

ANNEX 5 – NEW EMERGING TECHNOLOGIES SUBGROUP

Members of the GTAC New Emerging Technologies Subgroup are:

Reverend Dr Keith Denison (Chairman)
The Church in Wales
Diocese of Monmouth

Mrs Rosemary Barnes
Chief Executive
Cystic Fibrosis Trust
Kent

Dr Brenda Gibson
Department of Haematology
Hospital for Sick Children
Glasgow

Professor Ian Hart
UMDS
St Thomas' Hospital
London

Mrs Ann Hunt
Tuberous Sclerosis Association

Professor Norman C. Nevin
Queen's University of Belfast

Professor C Michael Steel
School of Biological & Medical Sciences
University of St Andrews

Mrs Irene Train
Formerly Director Public Health
Nursing
Clwyd Health Authority

ANNEX 6 – GENE THERAPY RESEARCH 1993–2000

GTAC No.	Protocol	Detail	Centre	Approval	Start Date	Vector	Gene	No. of patients
001	Adenosine deaminase gene transfer in a child with severe combined immunodeficiency syndrome	SCID-ADA	Institute of Child Health/Great Ormond Street Hospital	1-93	3-93 CLOSED	Retrovirus	ADA	1
002	Gene Therapy Research for Cystic Fibrosis	CF Nasal trial	Royal Brompton Hospital	3-93	9-93 CLOSED	Liposome	CFTR	15
003	A pilot study of idiotypic vaccination for follicular B-cell lymphoma using a genetic approach	B-cell lymphoma	MRC Cambridge	7-93	11-94 CLOSED	Plasmid	anti-idiotype immunoglobulin	7
004	Use of gene transfer to determine the role of tumour cells in bone marrow used for autologous transplantation and the efficiency of immunomagnetic "purging" the bone marrow	Neuroblastoma	ICRF Bristol	2-94	Withdrawn	Retrovirus	LNL-6/neo G1N-neo	–
005	Gene Therapy for metastatic melanoma: Assessment of expression of DNA constructs directly injected into metastases	Metastatic melanoma	ICRF Oxford	5-94	6-95	plasmid	IL-2	13
006	The treatment of metastatic malignant melanoma with autologous melanoma cells that have been genetically engineered to secret IL-2	Metastatic melanoma	Institute of Cancer Research/Royal Marsden Hospital	2-94	10-94 CLOSED	Retrovirus	IL2	12
007	Towards gene therapy for cystic fibrosis	CF Nasal trial	Oxford/Cambridge	2-94	5-95 CLOSED	Liposome	CFTR	12
008	Gene Therapy Research for Cystic Fibrosis	CF Nasal trial	Edinburgh	5-94	6-95	Liposome	CFTR	16

GTAC No.	Protocol	Detail	Centre	Approval	Start Date	Vector	Gene	No. of patients
009	Gene Therapy Research for Cystic Fibrosis	CF Lung trial	Royal Brompton Hospital	9-94		Liposome	CFTR	–
010	Transfer of the Human Multi-drug Resistance Gene into the Haemopoietic Cells of Patients Undergoing High Dose Therapy and Autologous Stem Cell Transplantation	Lymphoma	University College London Medical School	12-94	10-95 CLOSED	Retrovirus	MDR-1	3
011	Genetic prodrug activation therapy for breast cancer	Breast Cancer	Hammersmith Hospital	10-95	10-95 CLOSED	plasmid	Cytosine deaminase	12
012	Use of a recombinant vaccinia virus for therapy of cervical cancer	Cervical Carcinoma	University of Wales, Cardiff	6-95	9-95 CLOSED	Vaccinia virus	TA-HPV	1+8
012A	Use of a recombinant Vaccinia vaccine (TA-HPV) to treat Cervical intraepithelial neoplasia III	Cervical intraepithelial neoplasia III	University of Wales, Cardiff	5-96	9-96	Vaccinia virus	HPV E6 and E7	12
012B	Use of a recombinant Vaccinia vaccine (TA-HPV) to treat Cervical intraepithelial neoplasia III	Cervical intraepithelial neoplasia III	University of Wales, Cardiff/University of Manchester	8-97	1-98 CLOSED	Vaccinia virus	HPV E6 and E7	8
012C	Use of recombinant Vaccinia vaccine (TA-HPV) to treat Vulval intraepithelial neoplasia III	Vulval Intraepithelial Neoplasia III	St Mary's Hospital, Manchester	1-00	2-00	Vaccinia virus	HPV E6 and E7	3
012D	Use of a recombinant Vaccinia vaccine (TA-HPV) to treat Ano-genital intraepithelial neoplasia III	Ano-genital intraepithelial neoplasia III	Addenbrooke's Hospital, Cambridge	4-00	–	Vaccinia virus	HPV E6 and E7	–
013	A proposal to study the efficacy of transplantation of autologous retroviral transduced bone marrow in patients homozygous for the W402X mutation	Hurlers Syndrome	Royal Manchester Children's Hospital, Manchester	12-95	5-97	Retrovirus	pLX	3

GTAC No.	Protocol	Detail	Centre	Approval	Start Date	Vector	Gene	No. of patients
014A	Phase I, Open-Label, Dose-Escalation Trial of Intra-Tumoural Injection with an E1B Attenuated Adenovirus ONYX-015, into Recurrent and Locally Advanced p53(-) Squamous Cell Tumours of the Head and Neck	Head and Neck Cancer	Beatson Oncology Centre, Glasgow	1-96	3-96 CLOSED	Adenovirus	E1B deleted	30
014B	A Phase II trial of intravenous cisplatin, 5-FU and intratumoural injection with ONYX-015 into recurrent, chemotherapy naïve squamous cell tumours of the head and neck	Head and Neck Cancer Phase II Study	Beatson Oncology Centre, Glasgow	7-97	7-97 CLOSED	Adenovirus	E1B deleted	30
014C	Phase I, Open-Label, Dose-Escalation Trial of Intraperitoneal Injection with an E1B Attenuated Adenovirus in patients with recurrent/refractory ovarian carcinomas	Recurrent/refractory ovarian cancer	Beatson Oncology Centre, Glasgow	2-97	3-97	Adenovirus	E1B deleted	12
015	Towards gene therapy for Cystic Fibrosis	CF Nasal Trial	Oxford, Cambridge, Leeds & Manchester	5-96	7-96	Liposome	CFTR	11
016	Phase I study in patients with recurrent metastatic squamous cell carcinoma of the head and neck using SCH 58500 (rAd/p53)	Head and Neck Cancer	Institute of Cancer Research/Royal Marsden Hospital	9-96	12-96 CLOSED	Adenovirus	p53	–
017	Gene therapy for Cystic Fibrosis Delivery to nasal epithelium and lung by nebulisation.	CF Lung and Nasal Trial	Royal Brompton Hospital	11-96	11-96	Liposome	CFTR # 67	16

GTAC No.	Protocol	Detail	Centre	Approval	Start Date	Vector	Gene	No. of patients
018	A Phase I dose-escalation study of intratumoural injection with modified HSV Type I (ICP 34.5-) into recurrent malignant glioma	Glioblastoma	Beatson Oncology Centre, Glasgow	12-96	10-97 CLOSED	HSV	ICP34.5 deleted	9
018A	A Phase I dose-escalation study of intratumoural injection with modified HSV Type I (ICP 34.5-) into primary malignant glioma	Glioblastoma	Beatson Oncology Centre, Institute of Neurological Sciences, Glasgow & Queen Elizabeth Hospital, Birmingham	7-99			ICP34.5 deleted	7
019	GTI 0115 radiation and infection of murine cells producing HSV TK vector followed by intravenous ganciclovir against the efficacy of surgery and radiation in the treatment of newly diagnosed previously untreated glioblastoma (tumour site).	Glioblastoma	Beatson Oncology Centre, Glasgow/ Institute of Neurological Sciences, Glasgow	3-97	Withdrawn	Retrovirus	TK	–
020	A clinical trial with Ad-5CMV-p53 vector in patients with ascites formation.	Gastrointestinal cancer/malignant cancer ascites	Royal Marsden Hospital, London	4-97		Adenovirus	P53	1
021	Phase II study of immunotherapy of advanced breast cancer by repeated intramuscular injection of recombinant vaccinia viruses containing sequences coding for human MUC-1 and IL2 (TG1031).	Breast Cancer	Guy's Hospital, London	11-97		Vaccinia virus	MUC-1 IL2	11

GTAC No.	Protocol	Detail	Centre	Approval	Start Date	Vector	Gene	No. of patients
022	A multiple ascending dose study evaluating the safety and the gene transduction into malignant cells after the administration of E1A-lipid complex by intra-peritoneal administration in patients with epithelial ovarian cancer who over express HER-2/neu.	Ovarian Cancer	The John Radcliffe Hospital, Oxford Guy's and St Thomas's Cancer Centre, London Royal Marsden Hospital, London. St George's Medical School, London.	9-97	1-98	Lipid complex	E1A HER2/ neu	22
023	A pilot study of recombinant CEA vaccinia virus vaccine with post vaccination CEA peptide challenge in combination with 5-fluorouracil and folinic acid in the treatment of colorectal cancer (Phase I subcutaneous).	Colorectal Cancer	Queen Elizabeth Hospital, Birmingham	3-98	–	Vaccinia virus	CEA	–
024	A phase I study of intraperitoneal administration of a replication deficient adenovirus carrying a nitroreductase gene in ovarian cancer patients.	Ovarian Cancer	City Hospital NHS Trust and University Hospital NHS Trust Birmingham	3-98	–	Adenovirus	Nitroreductase	–
025	A multiple ascending dose study evaluating the safety and gene transduction into malignant cells after administration of E1A-lipid complex by intratumoural injection with unresectable or metastatic head and neck tumours.	Head and Neck	Royal London Hospital/Charing Cross Hospital	–	Withdrawn	Lipid complex	E1A	–

GTAC No.	Protocol	Detail	Centre	Approval	Start Date	Vector	Gene	No. of patients
026	A study of dose requirements, safety and local efficacy of intratumoural injection of the genetically modified non-virulent herpes simplex virus HSV ICP 34.5 negative mutant 1716 into accessible soft tissue nodules of secondary malignant melanoma.	Malignant Melanoma	Glasgow Western Infirmary and Southern General Hospital, Glasgow	9-98	1-99	HSV1716	ICP34.5 deleted	5
027	The use of MetXia-P450 for the treatment of advanced breast cancer (Phase I/II intratumoural).	Breast Cancer	The Churchill Oxford	10-98	2-00	Retrovirus	Cytochrome P450	8
028	A phase I/II study of hepatic artery infusion with WTP53-CMV-AD in primary metastatic malignant liver tumours.	Liver Cancer	Hammersmith Hospital, London	2-99	–	Adenovirus	p53	–
029A	A Phase I/II pilot study of idiotypic vaccination for follicular B-cell lymphoma using a genetic approach (i.m.).	B-cell lymphoma	Royal Bournemouth Hospital and Royal South Hampshire Hospital, Southampton	5-99	11-99	Plasmid	Idiotypic DNA vaccination	6
029B	A pilot study of donor idiotypic vaccination for the purpose of targeted post-transplant immunotherapy following allogeneic bone marrow transplantation for multiple myeloma	Multiple Myeloma	Royal Bournemouth Hospital and Royal South Hampshire Hospital, Southampton	5-00	8-00	Plasmid	Idiotypic DNA vaccination	5
029C	Phase I/II Study of Idiotypic vaccination for multiple myeloma using a genetic approach (MMIFTT)	Multiple Myeloma	Royal Bournemouth Hospital and Royal South Hampshire Hospital	4-00	–	Plasmid	Idiotypic DNA vaccination	–

GTAC No.	Protocol	Detail	Centre	Approval	Start Date	Vector	Gene	No. of patients
029D	Phase I/II Study of Idiotypic vaccination for Chronic Lymphocytic Leukaemia Using a Genetic Approach (CLLIFTT)	Chronic Lymphocytic Leukaemia	Royal Bournemouth Hospital and Royal South Hampshire Hospital	4-00	8-00	Plasmid	Idiotypic DNA vaccination	3
030	Use of a retrovirus carrying human cytochrome p450 for the treatment of ovarian cancer (Phase I intra-abdominal).	Ovarian Cancer	Northern General Hospital, Sheffield	2-00	8-00	Retrovirus	Cytochrome P450	2
031	Gene directed enzyme prodrug therapy for the treatment of head and neck cancer (Phase I intratumoural)	Head and Neck Cancer	CRC Institute for Cancer Studies, University of Birmingham	7-99	–	Adenovirus	Nitroreductase	–
032	Gene directed enzyme prodrug therapy for the treatment of liver cancer (Phase I intratumoural)	Liver Cancer	CRC Institute for Cancer Studies, University of Birmingham	7-99	–	Adenovirus	Nitroreductase	–
033	Phase I trial of immunotherapy with adenovirus-interferon-γ in malignant melanoma (intratumoural)	Malignant Melanoma	St. George's Hospital	7-99	1-00	Adenovirus	IFN-γ	1
034	A phase II/III trial of chemotherapy alone versus chemotherapy plus Adp53 in ovarian and primary intraperitoneal cancer (intraperitoneal)	Ovarian Cancer	Royal Marsden Hospital/ Christie Hospital/ CRC Institute for Cancer Studies/ John Radcliffe Hospital	7-99	–	Adenovirus	p53	–
035	Phase II trial of pre-operative intratumoural injection with an E1B attenuated adenovirus in patients with resectable head and neck tumours	Head and Neck Cancer	Beatson Oncology Centre, Glasgow	7-99	11-99	Adenovirus	E1B deleted	1

GTAC No.	Protocol	Detail	Centre	Approval	Start Date	Vector	Gene	No. of patients
036	The safety and effects of Ad5.1 mediated human FGF-4 gene transfer in patients with peripheral arterial occlusive disease (PAOD) Fontaine stage III (Phase I i.m.)	Peripheral Arterial Occlusive Disease	St George's Hospital, London	10-00	–	Adenovirus	FGF-4	–
037	A Phase III study of quadruple HAART followed by double-blind randomisation to HIV vaccination with ALVAC-HIV and Remune or placebo	HIV	Chelsea & Westminster Hospital, Royal Free Hospital, London Brighton General Hospital University Hospital of Wales, Cardiff	7-00	–	Canarypox	HIV-1 *env, gag*	–
038	A Phase I, open label, dose escalation trial to assess the safety and immunogenicity of DISC-GMCSF in patients with mestatatic melanoma	Malignant melanona	Churchill Hospital, Oxford Royal Marsden Hospital, London	5-00	–	HSV-2	hGMCSF	–
039	Gene therapy protocol for the evaluation of the safety, biodistribution and efficacy of Trovax in patients with metastatic colorectal cancer (Phase I i.m.)	Colorectal cancer	Christie Hospital NHS Trust, Manchester	10-00	–	Vaccinia	Human oncofoetal antigen 5T4	–
040	A Phase I dose escalation trial of an E1B attenuated adenovirus as an intravesical therapy for recurrent superficial/muscle invasive bladder cancer	Bladder cancer	St James's University Hospital, Leeds	Conditional approval 7-00	–	Adenovirus	E1B deleted	–

GTAC No.	Protocol	Detail	Centre	Approval	Start Date	Vector	Gene	No. of patients
041	Randomised multi-centre trial of MVA-MUC-1-IL-2 in women with metastatic breast cancer (Phase II i.m.)	Breast cancer	Guy's Hospital, London	Pending	–	Vaccinia	MUC-1, IL-2	–
042	Phase I study of melanoma poly-epitope DNA and melanoma poly-epitope modified vaccinia Ankara in patients with melanoma	Melanoma	The Churchill Hospital, Oxford	Conditional approval 7-00	–	Vaccinia	Mel3 (melanoma antigens)	–
043	A phase I/II trial of polyHER2neu-a polyepitope DNA vaccine encoding HER-2 epitopes in the treatment of epithelial cancers (i.m.)	Breast cancer	St James's University Hospital, Leeds	Under consideration	–	Plasmid	HER-2 epitopes	–

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Produced by Department of Health
22888 1p 1.25k Dec 00 (ABBA)
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